Cobalamin derivatives

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Inventor(s):
Applicant(s): MERCK & CO INC
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EC Classification: C07H23/00C
Equivalents: CH385873, SE304004

Abstract

The Specification comprises amino acid cobalamins of which those derived from glycine, lysine, aspartic acid, alanine, serine, cysteine, phenylalamine, tryptophane, histidine, methionine, valine, leucine, arginine, glutamic acid, and proline are specified. These compounds may be prepared by intimately contacting hydroxocobalamin and an amino acid in aqueous solution and then adding acetone to precipitate the product in crystelline form, alternatively the aqueous solution is evaporated by freeze drying. The compounds may be mixed with a solid carrier such as lactose, starch, sugar, stearic acid, magnesium stearate or gelatin or with a liquid such as water or benzyl alcohol to give compositions which give high prolonged serum levels on administration.ALSO:A medicinal preparation comprises an amino acid cobalamin and a pharmacologically acceptable carrier therefor. Specified cobalamins are those derived from glycine, lysine, aspartic acid, alanine, serine, cysteine, phenylalanine, tryptophane, histidine, methionine, valine, leucine, arginine, glutamic acid and proline; and they may be made according to the method described in Division C2. The carrier may be lactose, starch, sugar, stearic acid, magnesium stearate, or gelatin, or a liquid such as water or benzyl alcohol. The compositions may be made up in dosage units of 1 to 2500 mlg. of cobalamin activity.

944,428

PATENT SPECIFICATION

NO DRAWINGS

944,428

Date of Application and filing Complete Specification: April 1, 1960.

No. 11585/60.

Application made in United States of America (No. 804,145) on April 6, 1959.

Complete Specification Published: Dec. 11, 1963.

Index at acceptance:—Classes C2, V6; A5, B(2G, 2S).

International Classification:—C 07 d (A 61 k).

COMPLETE SPECIFICATION

Cobalamin Derivatives

We, MERCK & CO. INC., a corporation duly organised and existing under the laws of the State of New Jersey, United States of America, of Rahway, State of New Jersey, United States of America, do hereby declare the invention, for which we pray that a patent may be granted to us, and the method by which it is to be performed, to be particularly described in and by the following statement:—

This invention relates to cobalamin derivatives. More particularly it provides amino acid cobalamins, methods of preparing these cobalamin derivatives and compositions containing these cobalamin derivatives.

Vitamin B—12, which is also called cyanocobalamin, is known to be essential for erythrocyte maturation, and therapy with cyanocobalamin is indicated in anaemias resulting from its improper absorption and utilization. Thus, in the treatment of pernicious anaemia, cyanocobalamin is administered parenterally by subcutaneous or intramuscular injections. For this purpose aqueous solutions of vitamin B—12 in suitable vehicles are used. However, improved forms of cobalamin which would provide higher serum levels of cobalamin have been sought.

It is an aim of the present invention to provide improved cobalamin products producing higher serum levels of cobalamin on administration.

It has now been found that amino acid-cobalamins are valuable sources of cobalamin activity and possess the unexpected advantage that they are absorbed to a greater extent than cyanocobalamin. Thus, clinical tests show that these cobalamins give higher blood levels upon administration, and also apparently give higher prolonged serum levels of cobalamin.

There is therefore provided, according to the invention, a composition comprising an amino acid cobalamin and a pharmacologically acceptable carrier therefor.

The amino acid cobalamins are conveniently prepared by intimately contacting hydroxocobalamin and an amino acid in an aqueous solution. In general, the amino acid cobalamin compound is readily recovered from the resulting reaction mixture by adding a suitable miscible solvent such as acetone whereby the cobalamin precipitates from the solution in crystalline form and can be readily recovered, as for example by filtration. Alternatively, the amino acid cobalamin compound is recovered by evaporating the aqueous solution containing the molar equivalents of hydroxocobalamin and the amino acid, as for example by freeze drying.

Thus, in brief, there is provided according to the invention a process for preparing an amino acid cobolamin which comprises intimately contacting hydroxocobalamin and an amino acid in aqueous solution and recovering the amino acid cobolamin from the reaction mixture.

The following examples are illustrative of the methods by which these amino acid cobalamin compounds can be prepared:

EXAMPLE I

Glycine cobalamin

Hydroxocobalamin in an amount equivalent to 200 mg. of anhydrous weight, was dissolved in 40 ml. of water. To this solution was added 12.5 mg. of glycine. 375 ml. of acetone was added and the product allowed to crystallize. The crystals were isolated by filtration and dried *in vacuo* at room temperature. The product, which weighed 125 mg., contained 7.5 per cent volatiles and assayed 86.5 percent Vitamin B—12 (anhydrous basis) by isotope dilution assay. When correction is made for ratio of the molecular weights of cyanocobalamin and the glycine cobalamin the purity is *ca.* 90 per cent.

In a similar manner aspartic acid cobalamin is prepared by combining aspartic acid and hydroxocobalamin in aqueous solution and adding acetone.

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ERRATA

SPECIFICATION No. 944,428

Page 1, lines 48 and 55, *for* "cobalamin" *read* "cobolamin"
Page 2, line 11, *for* "cadculated" *read* "calculated"
Page 2, line 51, *for* "lactoose" *read* "lactose"
Page 3, 1st Table, *for* "Cyanocabalamin" *read* "Cyanocobalamin"

THE PATENT OFFICE
19th October 1964

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